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# CELLULAR AND MOLECULAR IMMUNOLOGY

SECOND EDITION

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T lymphocytes play a central role in specific immune responses to protein antigens. In Chapter 5, we introduced the concept that the physical forms of antigens recognized by T cells are actually peptide fragments that are derived from protein antigens and are bound to cell surface proteins encoded by genes of the major histocompatibility complex (MHC). Peptides bound to class I MHC molecules are typically derived from proteins synthesized in the cell that displays them (i.e., "endogenous antigens") and are recognized by $CD8^+$ T cells, which are usually cytolytic T lymphocytes (CTLs). CTLs provide a major host defense mechanism against intracellular microbes. In contrast, peptides derived from proteins in the extracellular environment ("exogenous antigens") are displayed in association with class II MHC molecules and are recognized by $CD4^+$ T cells, which are usually helper T lymphocytes. Helper T cells are required for the induction of humoral and cell-mediated responses, which are most effective in eliminating extracellular pathogens. In this chapter, we will describe in greater detail the characteristics of the peptide-MHC molecule complexes, the nature of the cells that form and display these complexes, and the mechanisms by which cells convert endogenous and exogenous protein antigens to peptides that can bind to MHC molecules. The activation and effector mechanisms of T cell subsets that occur subsequent to recognition of peptide-MHC complexes will be discussed in later chapters.

## CHARACTERISTICS OF ANTIGEN RECOGNITION BY T LYMPHOCYTES

Our current understanding of T cell antigen recognition is the culmination of a vast amount of work that began with studies of the physicochemical forms of antigens that stimulated cell-mediated immunity. These studies led to the discovery that cells other than T lymphocytes play an obligatory role in T cell activation by foreign antigens, and later to the elucidation of the function of MHC molecules in T cell antigen recognition.

## The Forms of Antigens Recognized by T Lymphocytes

The specificity of T lymphocytes for complexes of peptides and MHC molecules determines several characteristics of T cell antigen recognition, which differ in fundamental ways from antigen recognition by antibody molecules.

1. *T lymphocytes recognize only peptides*, whereas B cells can specifically recognize peptides, proteins, nucleic acids, polysaccharides, lipids, and small chemicals. As a result, T cell–mediated immune responses are induced only by protein antigens (the natural source of foreign peptides), whereas humoral immune responses are seen with protein and non-protein antigens. Some T cells are specific for chemically reactive forms of haptens such as dinitrophenol. In these situations, it is likely that the haptens bind to cell surface proteins, including MHC molecules, and peptides containing these hapten conjugates are recognized by T cells.

2. *T cells recognize only linear determinants of peptides defined predominantly by primary amino acid sequences* that assume extended conformations within the peptide-binding clefts of MHC molecules. In contrast, B cells specific for protein antigens may recognize conformational determinants that exist when proteins are in their native tertiary (folded) configuration or determinants that are exposed by denaturation or proteolysis. Thus, when an animal is immunized with a native protein, the antigen-specific T cells that are stimulated will respond to denatured or even proteolytically digested forms of that protein. In contrast, antibodies produced by B cells after immunization with the native protein react only with the native protein (Table

**TABLE 6–1. Qualitative Differences in Antigen Recognition by T and B Lymphocytes**



| Immunizing Antigen | Secondary Antigen Exposure | Secondary Immune Response: *B Cell–Mediated (Antibody Production)* | Secondary Immune Response: *T Cell–Mediated (Delayed-Type) Hypersensitivity* |
|---|---|---|---|
| Native protein | Native protein | + | + |
| Denatured protein | Native protein | – | + |
| Native protein | Denatured protein | – | + |
| Denatured protein | Denatured protein | + | + |

Antigen recognition by T and B lymphocytes is qualitatively different. In an immunized animal, B cells are specific for conformational determinants of the immunogen and, therefore, distinguish between native and denatured protein antigens. T cells, however, do not distinguish between native and denatured protein antigens because T cells recognize linear epitopes on short peptides derived from the intact proteins by proteolysis.

6–1). Consistent with this difference in the nature of antigenic determinants for T and B cell recognition is the finding that T cell responses to a soluble antigen cannot be inhibited using antibodies specific for conformational determinants of that antigen, whereas antigen recognition by B cells can be competitively inhibited by such antibodies.

3. *T cells recognize and respond to foreign peptide antigens only when the antigen is attached to the surfaces of other cells*, whereas B cells and secreted antibodies bind soluble antigens in body fluids or cell surface antigens. This is because MHC molecules form part of the complex that T cells recognize, and these molecules are cell surface–bound integral membrane proteins. The display of peptide-MHC complexes in a form that can be recognized by T cells is called **antigen presentation.** Cells that display antigens in this form are called **antigen-presenting cells (APCs).** The properties and functions of APCs are discussed later in the chapter. Although historically the term APC has most often been used to describe cells that present antigen to $CD4^+$ helper T lymphocytes, it is now appropriate to describe target cells of CTL lysis as APCs as well, since CTLs also recognize peptide-MHC complexes on the surface of these target cells.

## Physicochemical Features of Peptide-MHC Complexes

In order to stimulate T cell responses, peptides derived from protein antigens must bind to MHC molecules and must remain stably bound long enough to allow specific T cells to engage the complex. We will first describe the characteristics of the peptide-MHC complexes that T cells recognize, and later we will describe how these complexes are formed. The structural basis for peptide binding to both class I and class II MHC molecules has been analyzed by three approaches: (1) binding assays of peptides to purified MHC molecules in cell-free solutions; (2) x-ray crystallographic analyses of purified MHC molecules with bound peptides; and (3) amino acid analysis of peptides eluted from MHC molecules purified from cell membranes. The following are the main features of MHC-peptide interactions elucidated by these approaches:

1. *The association of antigenic peptides and MHC molecules is a saturable, low-affinity interaction ($K_d$ = $10^{-6}$ M) with a slow "on rate" and a very slow "off rate."* These features were determined first by the techniques of equilibrium dialysis (see Chapter 3 and Fig. 6–1) and

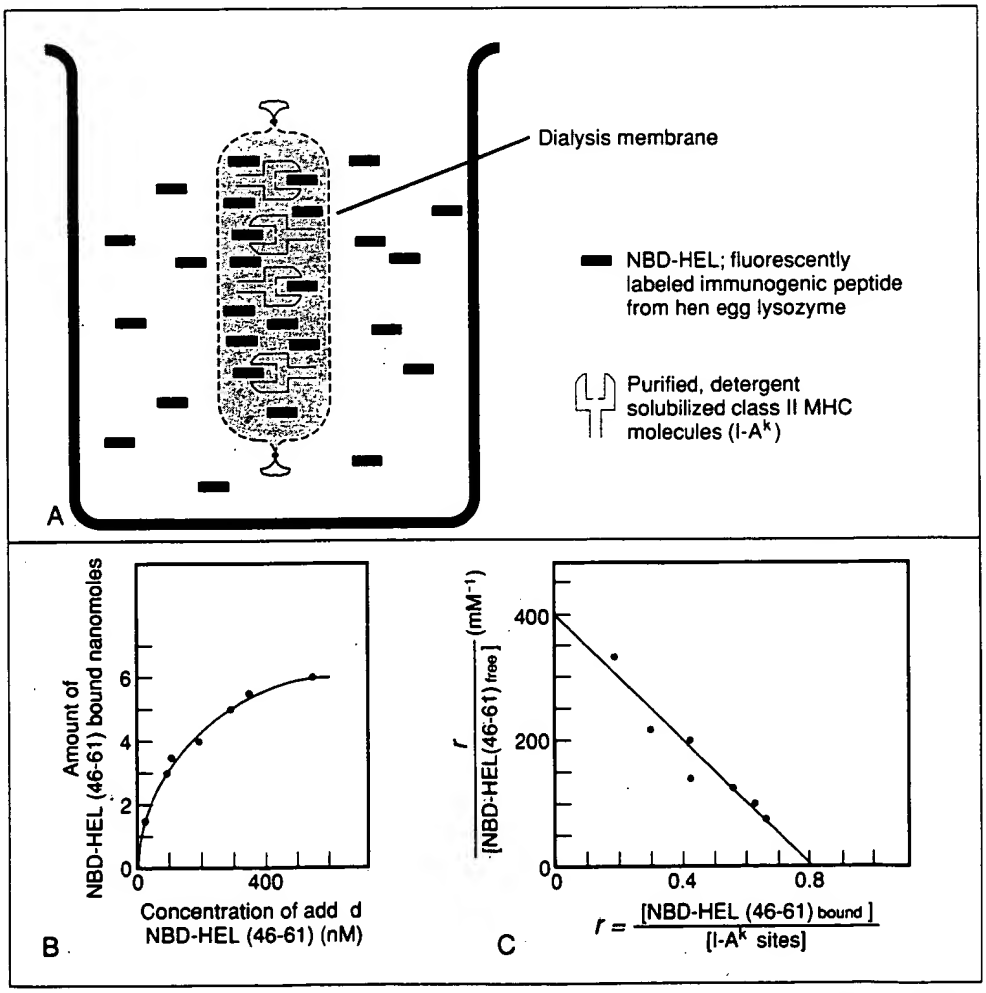


***FIGURE 6–1. Demonstration of peptide binding to MHC molecules by equilibrium dialysis.*** *Purified I-A$^k$ class II MHC molecules bind a peptide fragment of hen egg lysozyme (HEL), HEL(46–61), that is labeled with a fluorescent marker (NBD), which allows the concentration of the peptide to be determined (A). Analysis of the amount of HEL bound (i.e., the concentration within the dialysis membrane minus the concentration outside) at varying concentrations of peptide shows that the binding is saturable (B). Scatchard analysis shows that each I-A$^k$ molecule has approximately one binding site (X-axis intercept), and the dissociation constant ($K_d$) is approximately 1 × $10^{-6}$ M (calculated from the slope of the line). In this plot, r represents the number of peptide molecules bound to each MHC molecule when there is an excess of peptide (C). Note that HEL(46–61) is known to be presented in association with I-A$^k$ molecules. (Modified with permission from Babbitt, B. P., P. M. Allen, G. Matsueda, E. Haber, and E. R Unanue. Binding of immunogenic peptides to Ia histocompatibility molecules. Nature 317:359–361, 1985. Copyright © 1985, Macmillan Magazines Ltd.)*